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ACUTE T-2 INTOXICATION: PHYSIOLOGIC CONSEQUENCES
AND NEW THERAPEUTIC APPROACHES

ANNUAL REPORT

ALAN I. FADEN

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Trichothecene mycotoxins have been implicated in both naturally occurring diseases and chemical attacks on civilian and military personnel. Yet surprisingly little is known of the acute pathophysiological changes produced by ~~these substances~~. Symptoms reported following human attacks include a preponderance of autonomic symptoms, as well as blurred vision and convulsive movements, suggestive of involvement of the central nervous system. In experimental animals, a shock-like state accompanied by either paraplegia or ascending paralysis has been observed in several species. Taken together, these human and animal observations suggest that a major factor leading to death in cases of acute exposure may result from centrally mediated cardiovascular and/or respiratory depression.

Dose-response toxicology studies for T-2 toxin in the awake guinea pig demonstrated no significant mortality and only minimal morbidity at doses below 0.75 mg/kg; however, mortality rate was 37% for animals given a dose of 1 mg/kg i.v., and 73% for animals given

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a dose of 2 mg/kg i.v. Two hours after higher doses of T-2, animals developed significant bradycardia which progressed over the next 10 hours. Hypotension developed more gradually, being only mild (-20 mm Hg) at 12 h post-injection, with profound hypotension (to 20-30 mm Hg) by 24 h post-injection. Accompanying these cardiovascular changes was a metabolic acidosis, yet associated with normal PO_2 and mild to moderate reduction in PCO_2. A very substantial dose-related increase of plasma catecholamines was also observed over the first 6 h post-injection. The hypotension proved resistant to relatively high doses of N-methylatropine and naloxone. In contrast, a single i.v. dose of TRH (2 mg/kg) caused a substantial increase in mean arterial pressure which persisted over one hour.

The present findings indicate that T-2 toxin, at high doses, produces profound bradycardia and hypotension. The relative lack of effect of N-methylatropine, combined with the extremely large increase in plasma catecholamines, suggests that the central nervous system, and particularly central parasympathetic pathways, may play a critical role in mediating the shock state. The beneficial effects of TRH on blood pressure indicate that continuous infusions of TRH, or utilization of TRH-analogs with longer half-lives, may have a beneficial action on the cardiodepression which accompanies T-2 toxin administration.

SUMMARY

Trichothecene mycotoxins have been implicated in both naturally occurring diseases and chemical attacks on civilian and military personnel. Yet surprisingly little is known of the acute pathophysiological changes produced by these substances. Symptoms reported following human attacks include a preponderance of autonomic symptoms, as well as blurred vision and convulsive movements, suggestive of involvement of the central nervous system. In experimental animals, a shock-like state accompanied by either paraplegia or ascending paralysis has been observed in several species. Taken together, these human and animal observations suggest that a major factor leading to death in cases of acute exposure may result from centrally mediated cardiovascular and/or respiratory depression.

This is the first annual progress report (truncated, covering the period 1 January - 15 August 1983). The primary objective of this research was to gain information regarding the potential mechanism by which T-2 toxin produces its pathophysiological actions, with particular focus on the possible role of the central nervous system in mediating these effects. A second objective was to evaluate whether the resulting shock state was amenable to recently developed pharmacotherapies which have proved effective in other shock states of central origin.

Most of these initial studies have utilized an awake, freely moving guinea pig model, in which the animal has been previously instrumented. Dose-response toxicology studies demonstrated no significant mortality

and only minimal morbidity at doses below 0.75 mg/kg. In the first 24 hour period post-injection, however, mortality rate was 37% for animals given a dose of 1 mg/kg i.v., and 73% for animals given a dose of 2 mg/kg i.v. Two hours after having received these higher doses, animals developed significant bradycardia which progressed over the next 10 hours, such that there was a decline of some 100 beats/min at 12 h post-injection. Hypotension developed more gradually, being only mild (-20 mmHg) at 12 h post-injection, with profound hypotension (to 20 - 30 mmHg) by 24 h post-injection. Accompanying these cardiovascular changes, particularly at the higher doses, was a substantial metabolic acidosis, yet associated with normal pO_2 and mild to moderate reduction of pCO_2. A very substantial increase of plasma catecholamines was also observed over the first six h post-injection; these were clearly related to dose of the toxin, with more than a 20-fold increase observed six hours following a T-2 dose of 2 mg/kg. Both the hypotension and bradycardia proved resistant to relatively high doses of N-methylatropine, which does not cross the blood brain barrier; similary, the opiate receptor antagonist naloxone proved ineffective in modifying either the heart rate or blood pressure response. In contrast, a single i.v. dose of TRH (2 mg/kg) caused a substantial increase in mean arterial pressure which persisted over one hour.

Taken together, the present, preliminary findings indicate that T-2 toxin, at high doses, produces profound bradycardia and hypotension. The relative lack of effect of N-methylatropine, combined with the extremely large increase in plasma catecholamines, suggests that the central nervous system, and particularly central parasympathetic pathways, may play a critical role in mediating the shock state. The beneficial effects of TRH on blood pressure indicate that continuous infusions of TRH, or utilization of TRH-analogs with longer half-lives, may have a beneficial action on the cardiodepression which accompanies T-2 toxin administration. In addition to the above studies, preliminary studies have begun to further assess the autonomic changes produced by the T-2 toxin. These have included development of a Doppler-based method to continuously assess blood flow in discrete vascular beds (such as the splanchnic, renal, etc.) in chronically instrumented awake animals. Such technology should permit a more precise delineation of the pathophysiological effects of the T-2 toxin and of the potential therapeutic action of TRH.

FOREWORD

Citations of trade names in this report do not constitute an official Department of the Army endorsement or approval of the use of such items.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laborato.y Animal Resources, National Research Council (DHEW Publication No. [NIH] 78-23, Revised 1978).

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This is the first annual report submitted under contract #USAMRDC 08040-82 and covers the period 1 January - 15 August 1983. Much of this period has been devoted to development of a laboratory and the animal models to be studied; namely fully instrumented, awake, freely moving guinea pigs and rats. Studies reported therefore include predominantly preliminary descriptions of the pathophysiological effects of the toxin, including: (1) dose-response effects in the guinea pig; (2) cardiovascular changes; (3) arterial blood gas changes; and (4) changes in plasma catecholamines. In addition, preliminary information is provided regarding potential therapeutic effects of three classes of agents: (1) anticholinergics; (2) opiate receptor antagonists; and (3) thyrotropin-releasing hormone.

Problem. Trichothecene mycotoxins, of which T-2 toxin is a particularly potent example, have been implicated in severe, naturally occurring, potentially fatal diseases of both man and animals following ingestion of contaminated grains.[1] More recently, evidence has been provided suggesting that trichothecenes, particularly the T-2 toxins, have been used in chemical attacks on both civilian and military populations.[2] Although the illness presents with striking autonomic features,[3,4] little is known about the pathophysiology of toxin-induced disease, particularly regarding the sequence and severity of specific autonomic changes.

The purpose of the present studies was to assess such autonomic changes, particularly with regard to the cardiovascular and respiratory systems, focusing on the potential role of the central nervous system in mediating this process. We have also evaluated in preliminary fashion several classes of substances which have recently been utilized to reverse cardiorespiratory depression of central origin.

BACKGROUND

Although the T-2 toxin and other trichothecenes affect a number of organ systems, neurologic manifestations with striking autonomic features are characteristic of both acute and chronic exposure.[3,4] A prototypic human disease following chronic exposure to T-2 toxin is associated in its early stages with excessive salivation, headache, dizziness, weakness, fatigue, tachycardia, fever and sweating.[3] In the second phase, palpitations, dilated pupils, increased and labile pulse pressure, hypotension and hypothermia have been reported.[3,4] In experimental animals, chronic oral administration of T-2 toxin produces weakness and/or ataxia, and dyspnea in both cats[5] and monkeys.[6] Death after chronic exposure, however, usually results from hemorrhage and/or infection secondary to bone marrow failure, although in the monkey,[6] death from respiratory failure has been reported. Following acute trichothecene intoxication, on the other hand, mortality appears likely to result primarily from neurological involvement directly, particularly from centrally mediated autonomic changes including cardiovascular and/or respiratory depression.[7-11] Acute parental administration of T-2 toxin to rats and guinea pigs produces a shock-like state with hypothermia accompanied by posterior paresis.[8] Similar results have been noted in acute T-2 experiments in swine,[9] chicks[10] and cats.[11] In the reports of human attacks,[2] victims developed dizziness, headache, blurred vision, confusion and weakness associated with shortness of breath, palpitations, nausea and vomiting. Although hemorrhage may occur, death ensues rapidly whether or not bleeding is present. Taken together, observations in animals and man suggest that neurologic, and particularly autonomic manifestations appear to play a major role in the morbidity and mortality which follows T-2 exposure. Despite this fact, detailed physiologic studies of the autonomic nervous system and other neurological consequences of acute trichothecene intoxication have been lacking.

Moreover, treatment for the mycotoxicoses, whether acute or chronic, is limited. Beyond removal from exposure and general medical support, little therapy is available. Since centrally mediated shock appears to play a critical role in the morbidity and mortality of acute intoxication, investigation of agents known to reverse other forms of centrally mediated shock seems logical. Since some of the symptoms are reminiscent of exposure to organophosphates,[2] which produces central cholinergic excess,[12] it would be of interest to evaluate the effect of anticholinergics following T-2 exposure. Moreover, cholinergic factors have been identified in other centrally mediated shock states.[13] More recently, central peptidergic systems have been implicated in multiple forms of shock,[14] and it has been demonstrated that opiate receptor antagonists and thyrotropin-releasing hormone can reverse shock associated with endotoxemia,[15-17] hypovolemia[17,18] or spinal cord injury.[19,20] TRH has also been found to block or reverse leukotriene-induced hypotension[21] and shock produced by platelet-activating factor.[22] The effectiveness of these agents in shock and the fact that they act centrally provided the rationale for their evaluation following

T-2 intoxication. The purpose of the present studies was, therefore, two-fold: (1) to detail the autonomic changes which occur following T-2 administration in animals, particularly with regard to the cardiovascular and respiratory systems; and (2) to evaluate several classes of pharmacotherapy which we have proved effective in other shock states of central origin.

MATERIALS AND METHODS

Following anesthesia (xylazine 4 mg/kg s.c. and ketamine 60 mg/kg i.m.), a femoral cutdown was performed under an operating microscope. PE 50 polyethylene catheters containing heparinized saline were introduced into the femoral artery and vein, threaded centrally and fixed by ligatures at the cutdown site. The peripheral (extravascular) portion of each catheter was threaded subcutaneously up the back to exit from a small skin incision in the posterior cervical region. The externalized portion of each catheter was then passed through a 20 cm length of protective spring wire, and the spring wires/catheters were anchored as a unit in an adhesive collar placed around the animal's neck. The spring wires/catheters were brought out through an opening in the animal's cage and the catheter ends occluded with 2[illegible] gauge needles connected to tuberculin syringes containing heparinized saline. The catheters were flushed with heparinized saline twice daily to maintain patency. At the time of study, the catheters were utilized for cardiovascular monitoring and drug administration. Studies were performed 24 hours or more after the surgery at which time the animals were fully awake and freely moving. This technique represents our own adaptation of the technique originally described by Chiueh and Kopin[23] for tail artery catheterization in rats. We have subsequently used it extensively in our laboratories for the study of cardiovascular function in both rats[15-18] and guinea pigs.[21,22]

T-2 toxin (supplied by USAMRIID) was administered i.v. at doses of 0.5, 0.75, 1.0 and 2.0 mg/kg. ABG's were measured on a Corning Model 165/2 pH/blood gas machine. The plasma was assayed for catecholamine levels by a radioenzymatic thin-layer chromatographic procedure described by DaPrada and Zurcher,[28] and by Weise and Kopin.[25] Samples were also taken for plasma leukotrienes.[26]

One group of animals (n=4) was pretreated with N-methylatropine, an anticholinergic compound which does not cross the blood brain barrier, at a dose of 2 mg/kg; subsequently, they were administered T-2 toxin at a dose of 2 mg/kg, and cardiovascular responses followed for 24 hours. Another group of animals was pretreated with N-methylatropine at 2 mg/kg, followed by a continuous i.v. infusion of 0.5 mg/kg/h for 24 h; they too received T-2 toxin at a dose of 2 mg/kg. Four animals were pretreated with naloxone at 1 - 5 mg/kg after T-2 toxin. Four guinea pigs were treated with TRH (2 mg/kg) after cardiovascular dynorphin produced by T-2 toxin (2 mg/kg).

In the awake guinea pig, T-2 toxin produced cardiorespiratory effects following doses of 0.5 or 0.75 mg/kg. However, the dose response curve was quite steep, with 1 mg/kg producing an LD of 37.5% and 2 mg/kg producing a mortality of 73% (Table 1). The earliest autonomic change was a significant bradycardia which was noted within the first two hours following injection;

MAP continued to decline until approximately 12 hours after injection, at which point the average heart rate was reduced from approximately 300 to 200 beats/min (Table 2). During the second 12 hour period following injection there was a slight recovery of heart rate. Blood pressure declined only modestly (approximately 20 mmHg) during the first 12 h, even at the highest doses; however, during the next 12 h there was a substantial reduction of MAP to approximately 20 - 30 mmHg at the higher doses of T-2 toxin (Table 2). Arterial blood gases showed a gradual [illegible]ne in pH, despite a moderate hypocarbia and pO_2 values which were actually elevated above baseline levels (Table 3). Plasma catecholamines showed a significant increase during the first six h post-injection and at the highest doses they reached levels as [illegible] as 40-fold higher than baseline (Table 4). The marked bardycardia observed appeared to be somewhat altered by pretreatment with N-methylatropine (Table 5), an anticholinergic which does not cross the blood brain barrier, but blood pressure was unaffected by this treatment. Each of four animals administered TRH at a dose of 2 mg/kg showed a prompt and substantial rise in mean arterial pressure. In three of the four animals, this change was sustained for more than one hour after a single bolus injection of TRH (Table 6). Changes in heart rate were more transitory and less pronounced. These TRH effects occurred at a time (4 - 6 h after T-2 toxin) when MAP and HR were declining rapidly in control animals, thus underscoring the nature of the TRH-induced cardioexcitation. In contrast to the beneficial effects of TRH, naloxone was without effect on either blood pressure or heart rate (data not shown).

CONCLUSIONS

The present studies, although still somewhat preliminary, have established the LD dose-response curve for T-2 toxin in the awake, freely moving guinea pig. We have demonstrated that bradycardia precedes other cardiovascular/respiratory changes. The bradycardia occurs despite the marked sympathetic stimulation as evidenced by the substantial increases in plasma catecholamines. N-methylatropine, which does not cross the blood brain barrier, had a partial effect on the heart rate, suggesting that part of the bradycardia is not of central origin. However, blood pressure changes were not altered by N-methylatropine, even when continuously administered. The opiate-receptor antagonist naloxone was without effect on either the blood pressure or heart rate changes after T-2 toxin. In contrast, TRH markedly reversed T-2-induced hypotension, with more modest and transitory effects on heart rate. Although T-2 toxin produced a metabolic acidosis, particularly at higher doses, there was no evidence of respiratory depression; indeed, pO_2 values were enhanced after high doses of T-2, even in the presence of profound hypotension.

RECOMMENDATIONS

It is our intention to extend the above findings by examining the effects of atropine and TRH-analogs (which have higher central potency and far longer half-lives) on the autonomic changes produced by T-2 toxin. Studies are now pending to evaluate central changes in plasma leukotrienes and plasma fibronectin, a vasoactive lipid and glycoprotein, respectively, which have been implicated in induction of other forms of shock. The potential secondary role for leukotrienes is particularly appealing, since this class of substances produce TRH-sensitive, naloxone-insensitive shock, as in the present studies. It is also our intention to apply advanced new micro-Doppler technology which we have been perfecting in the rat and which will permit continuous measurements in awake, freely moving animals of blood flow changes in discrete vascular beds. This will allow a better descriptive profile of the pathophysiological changes following the T-2 toxin and potential responses from pharmacologic agents. It is also our desire to examine in more detail the cardiac changes after T-2 toxin, by evaluating changes in cardiac output and stroke volume, utilizing a new thermodilution technology recently developed for use in small animals. Finally, studies during the second grant year will examine the brains in animals subjected to shock for specific pathological changes, and will begin to compare physiologic and pathological changes produced in the guinea pig with those produced in rat.

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TABLE 1

SURVIVAL (24 HR) AFTER T-2 TOXIN ADMINISTRATION
IN THE GUINEA PIG

T-2 DOSE mg/kg	N	ALIVE	DEAD
0.5	8	7 (87.5%)	1 (12.5%)
0.75	4	4 (100%)	0 (0%)
1.0	8	5 (62.5%)	3 (37.5%)
2.0	15	4 (26.6%)	11 (73.3%)

TABLE 2

CARDIOVASCULAR CHANGES FOLLOWING T-2 TOXIN ADMINISTRATION IN THE GUINEA PIG

A. MEAN ARTERIAL PRESSURE (mmHg)

T-2 DOSE mg/kg	TIME AFTER INJECTION				
	0	2 HR	4 HR	12 HR	24 HR
0.5	59.9 ±2.1	49.5 ±2.1	43.2 ±2.0	45.8 ±5.5	40.6 ±5.9
0.75	69.5 ±4.7	60.3 ±2.8	52.0 ±2.0	55.5 ±2.1	63.0 ±4.0
1.0	60.5 ±2.5	56.1 ±2.5	53.5 ±2.4	43.6 ±3.8	28.8 ±5.8
2.0	59.8 ±1.7	57.8 ±2.1	50.9 ±2.3	41.2 ±1.8	30.8 ±3.4

B. HEART RATE (Beats/min)

T-2 DOSE mg/kg	0	2 HR	4 HR	12 HR	24 HR
0.5	300.6 ±6.5	248.7 ±14.2	220.6 ±12.9	261.4 ±14.4	312.5 ±14.8
0.75	293.8 ±3.8	248.8 ±7.2	236.3 ±13.8	272.5 ±14.9	356.7 ±16.2
1.0	316.8 ±9.4	233.8 ±8.0	228.8 ±11.8	191.8 ±16.7	256.3 ±28.3
2.0	299.6 ±5.8	260.0 ±10.1	224.6 ±7.2	201.5 ±9.6	292.5 ±31.1

TABLE 3

ARTERIAL BLOOD GAS CHANGES AFTER T-2 TOXIN

T-2 Dose (mg/kg)	TIME AFTER INJECTION 0	2 HR	4 HR	6 HR
A. pH				
1.0	7.48 ±0.01	7.43 ±0.02	7.48 ±0.03	7.41 ±0.02
2.0	7.48 ±0.01	7.40 ±0.01	7.38 ±0.05	7.28 ±0.11
B. PO_2				
1.0	76.1 ±4.2	91.1 ±2.8	99.5 ±3.6	109.2 ± 8.4
2.0	72.6 ±4.2	94.7 ±5.6	110.7 ±5.2	118.3 ± 8.0
C. PCO_2				
1.0	31.7 ±0.8	29.8 ±0.8	33.8 ±1.6	35.2 ±2.0
2.0	30.3 ±1.3	28.7 ±0.5	29.2 ±2.3	25.8 ±4.6

TABLE 4

CHANGES IN PLASMA CATECHOLAMINES AFTER T-2 TOXIN

T-2 Dose (mg/kg)	TIME AFTER INJECTION 0	2 HR	4 HR	6 HR
A. Norepinephrine (pg/ml)				
1.0	581 ±250	837 ±426	2,287 ± 686	4,192 ±1,398
2.0	228 ± 43	1,273 ± 400	4,453 ±1,581	8,777 ±3,416
B. Epinephrine (pg/ml)				
1.0	201	563 ± 225	764 ± 213	2,193 ± 809
2.0	362	1,773 ± 784	6,008 ±2,348	14,439 9,104
C. Dopamine (pg/ml)				
1.0	650 ±114	500 ± 79	634 ± 163	728 ± 191
2.0	549	572 ± 31	1,036 ± 175	1,407 ± 427

TABLE 5

EFFECT OF PRE-TREATMENT WITH N-METHYL-ATROPINE
ON CARDIOVASCULAR CHANGES AFTER T-2 TOXIN (2 mg/kg)

A. Single Pre-treatment Dose (2 mg/kg).

	Time After Injection				
	0	2 HR	4 HR	12 HR	24 HR
MAP	62.1 ±3.0	62.0 ±3.5	56.0 ±2.1	23.5 ±0.5	--
HR	323.8 ±24.0	317.5 ±27.1	290.0 ±13.5	160.0 ±15.0	--

B. Pre-treatment (2 mg/kg) Followed by Infusion at 0.5 mg/kg/h.

	0	2 HR	4 HR	12 HR	24 HR
MAP	63.3 ±9.6	51.5 ±5.7	57.7 ±5.2	45.0 ±9.8	29.5 ±14.5
HR	315 ±13.4	340 ±4.6	325 ±2.5	275 ±5.0	225 ±125

TABLE 6

EFFECT OF TRH TREATMENT (2 mg/kg) ON
CARDIOVASCULAR CHANGES AFTER T-2 TOXIN

	Pre-TRH (4-6 h post T-2)	Time after TRH 1 min	10 min	30 min	60 min	120 min
MAP	46.6 ±5.4	75.6 ±5.4	66.6 ±3.8	61.2 ±4.6	54.6 ±7.2	50.9 ±8.6
HR	228.8 ±5.9	270.0 ±26.8	257.5 ±30.9	231.2 ±21.0	225.0 ±22.1	208.3 ±17.4